II. REMARKS

This Response is timely filed with a Request for Continued Examination (RCE) and the required fees. Applicant thanks the Examiner for indicating that the amendments in the November 2, 2009 Response were entered and that the written description rejection was withdrawn.

Claims 1-11 are pending in this application. Claims 2, 5, and 6 are withdrawn. By this Amendment, claim 4 is amended and claims 10-11 are added. Support for the amendments may be found in the specification and claims as originally filed. For example, the amendment to claim 4 and new claims 10-11 are supported by pages 13-14 of the specification, and compound II^C of the specification and claim 7. Applicant submits that no new matter is added.

Claims 1, 3, 4, 7, and 8 are rejected under 35 U.S.C. §103(a) as being unpatentable over Armour et al. (Arthritis and Rheumatism, 44(9):2185-92 (2001)) in view of Jang et al. (Free Radical Biology & Medicine, 24(9):1511-19 (1998)). Applicant respectfully traverses this rejection.

Applicant agrees with the Examiner that "Armour et al. does not specifically teach the method of treating degeneration of the cartilaginoid matrix comprising administering to a subject in need thereof an effective amount of one or more compounds or salts thereof having the formula (I), or the elected species (instant claim 1)" (final Office Action, page 9).

Applicant respectfully maintains that Jang et al. does not fulfill this deficiency of Armour et al., as Jang et al. does not teach or suggest the use of the presently claimed compounds to treat degeneration of the cartilaginoid matrix. In addition to the

previously filed remarks distinguishing Jang et al., Applicant respectfully submits that Jang et al. does **not** teach a protective effect of NO donors for the cartilage matrix.

In contrast, Jang et al. clearly discusses the role and effects of endogenous NO in cells. For example, each section of Jang et al. is discussed below:

a) "Arthritis" – This section concludes that "Here we aim to place the role of NO in the catabolic cascade of biochemical events that lead to arthritis." As such, this section clearly refers to the role of endogenous NO;

b) "Biochemistry of Nitric Oxide" – This section refers to metabolism of NO which is clearly endogenous;

c) "The Nitric Oxide Synthases" – The section discusses how NO is produced in cells by particular enzymes, nitric oxide synthases (NOS). As such, this section clearly refers to endogenous NO;

d) "Nitric Oxide Production in Diarthrodial Joints" – This section discusses the expression (production) of NOS in diarthrodial joins. Endogenous NO is the only subject;

e) "Regulation of Inducible Nitric Oxide Synthases" – This section describes the activity of NOS by the use of inhibitors listed at the end of the section. Endogenous NO is the only subject;

f) "Cytokines and Nitric Oxide in Chronic Inflammation" – NO induced by cytokines appears to be a novel mediator of inflammation playing a role in many cellular events of inflammation. The subject is clearly endogenous NO. The authors then refer to a study where a NO donor (exogenous NO), SNAP, increased the level of a cytokine TNF-α in specific cultured cells. Based on this finding the authors suggest that NO in

inflammation perpetuates the secretion of pro-inflammatory cytokines. The object is again endogenous NO. The results of the study with SNAP teach away from using NO donors in chronic inflammation as the NO donors increased the level of a cytokine that is a mediator of inflammation;

g) "Nitric Oxide in Human Rheumatoid Arthritis" – This entire section illustrates the negative effects of endogenous NO in rheumatoid arthritis;

h) " Nitric Oxide in Human Osteoarthritis" – This section discusses the presence of NOS and levels of NO (endogenous) in osteoarthritis-affected cartilages;

i) "Inflammatory Arthritis" – This section relates to studies in models of inflammatory arthritis. Administration of inhibitors of NOS (i.e., a decrease of endogenous NO) suppresses development of arthritis. Microbial products instead may increase the level of NOS in bovine and human osteoarthritic cartilage. The subject again is endogenous NO;

j) "iNOS Knockout Studies" – This section relates to studies in mice strains deficient of NOS. This section focuses on the role of endogenous NO;

k) "Cartilage Matrix Metabolism" – This section relates to the metabolism of cartilage matrix. In particular, this section discloses that "[i]n arthritis, an increased loss of proteoglycans leads to cartilage dysfunction and eventually, irreversible matrix degeneration . . . ";

l) "NO and Proteoglycans" – This section examines the role of endogenous NO in the synthesis and degradation of proteoglycans;

m) "NO and Proteinases" – This section analyses the role of endogenous NO in the activation of metalloproteases which are enzymes responsible for the degradation of

proteoglycans. There is only a reference to NO donors (page 1516, column 1, lines 5-8). This section discloses that in cell-free enzyme preparations, the NO donors did not affect enzyme activity;

n) "NO and Collagen" – This section discloses that exogenous NO inhibits the enzyme prolyl hydroxylase, which is responsible for collagen crosslinking. Non-crosslinked collagen undergoes intracellular proteolysis. In an extract of cells, SNAP, an exogenous NO donor, decreased the prolyl hydroxylase activities. As such, this section teaches away from the use of exogenous NO;

o) "NO and Cyclooxygenase" – This section analyses the effects of endogenous NO on COX, the enzymes responsible for inflammation. The experiments have shown opposing effects. Exogenous NO donors had a little effect on ovine COX preparations;

p) "NO and Apoptosis" – This section discloses that NO production in cartilage may induce chondrocytes apoptosis (cell death) even if there is no evidence *in vivo*; and

q) "Concluding Remarks" – This section refers to endogenous NO and states that there is mounting evidence for the role of NO in catabolic events (i.e., the negative effects discussed in the previous sections). Despite that, the authors note that there is also data that suggest a protective role of NO (endogenous NO) but the article does not disclose this data.

As such, each and every section of Jang et al., when viewed as a whole, is directed to endogenous NO, not an exogenous NO donor. Applicants respectfully maintain that there is no teaching or suggestion in Jang et al. that administration to a patient of NO donors in general, much less the compounds of the presently claimed invention, may increase the level of NO in cells and in particular cartilage cells, and

whether the effect could be protective for cartilage. In contrast, the majority of data reported in the article *in vivo* or in cell cultures refers to endogenous NO and demonstrates negative effects of NO in cartilage matrix. See, for example, the authors' conclusion of the "mounting evidence" for the role of NO in catabolic events. The limited data reported for NO donors (classical NO donors distinguishable from the compounds of presently claimed invention) teaches away from the presently claimed invention as it relates to *in vitro* preparations and shows no effect or negative effects on the enzyme activities. Accordingly, a person of ordinary skill in the art would not have combined the disclosures of Armour et al. and Jang et al., much less to achieve the presently claimed invention.

For at least the above reasons, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1, 3, 4, 7, and 8 under 35 U.S.C. §103(a) over Armour et al. in view of Jang et al.

Claim 9 is rejected under 35 U.S.C. §103(a) as being unpatentable over Armour et al. in view of Jang et al. as applied to claims 1, 3, 4, 7, and 8 above, and further in view of Gabalawy et al. (Arthritis Res. 4(suppl 3):S297-301 (May 9, 2002)). Applicant respectfully traverses this rejection.

Applicant agrees with the Examiner that "Armour et al. in view of Jang et al. does not specifically disclose the method wherein relapses of degeneration of the cartilaginoid matrix are reduced" (final Office Action, page 12).

Further to the remarks above, Applicant respectfully maintains that El-Gabalawy et al. does not satisfy the above-discussed deficiencies of Armour et al. and Jang et al.,

as El-Gabalawy et al. does not teach or suggest the use of the presently claimed compounds to treat degeneration of the cartilaginoid matrix.

For at least the above reasons, Applicant respectfully requests reconsideration and withdrawal of the rejection of claim 9 under 35 U.S.C. §103(a) over Armour et al. in view of Jang et al., and further in view of Gabalawy et al.

III. CONCLUSION

Applicant respectfully submits that this application is in condition for allowance and such action is earnestly solicited. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicant's undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.

In the event that this paper is not being timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fees for such an extension, together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account Number 01-2300, referencing Docket Number **026220-00055**.

Respectfully submitted,

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